REMARKS

Reconsideration of the Office Action mailed November 13, 2002, (hereinafter "instant Office Action"), entry of the foregoing amendments, withdrawal of the objection to claims 4-6 and rejection of claims 1-8, are respectfully requested.

In the instant Office Action, claims 1-8 are listed as pending and claims 1-8 are listed as rejected.

The Examiner has objected to claims 4-6 "under 37 CFR 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim. These claims depend from claim 1 which defines a method yet they do not contain any further limitations to as to the practice of such method". In response to this objection, Applicants have cancelled claims 4-6 without waiver or prejudice. Thus, the objection to claims 4-6 under 37 CFR 1.75(c) is moot and should be withdrawn.

The Examiner has rejected claims 1-8 under 35 U.S.C. §103(a) as being unpatentable over Buttle (Exp. Opin. Invest. Drugs (1996), 5(12):1583-1587) and Wilding (BMJ Volume 315, 18 October 1997, pp 997-1000). Applicants respectfully traverse this rejection. Applicants maintain the arguments that were submitted in the reply mailed October 8, 2002. The rejection as it applies to claims 4-6 is moot based upon the cancellation of claims 4-6.

The Examiner alleges that Buttle and Wilding teach that sibutramine and orlistat are drugs which are effective for the treatment of obesity, and that it would be obvious to combine one or more ingredients each of which was known to be useful for the same purpose in order to form a third composition for the same purpose. Buttle reviews the three drugs dexenfluramine, sibutramine and orlistat in detail. In the last section of the paper, entitled "Conclusion and Perspective" it is stated in the second paragraph:

> "The three drugs either recently approved for market, or accelerating towards approval, with many more in late stages of development (see Tables 1 and 2), are indicative of the intense research interest that the pharmaceutical industry has injected into this new area of therapy. Although these early therapies are not without their side-effects, and, thus, are generally not recommended for widespread use, further research may lead to better tolerated therapies, with

fewer associated risks. Furthermore, the wide variety of approaches under investigation could lead to future combination therapies."

The final sentence of this paragraph is a very broad-sweeping generalization. It does not provide motivation to a person skilled in the art to try the particular combination of sibutramine and orlistat and it does not suggest use of the combination for co-morbid conditions associated with obesity, wherein claims 1-3 are directed to the treatment of co-morbid conditions associated with obesity. Buttle also does not teach or suggest synergy between sibutramine and orlistat. Table 2 contains eight compounds and Table 1 contains three compounds. The number of possible permutations of a two-compound combination therapy from simply those compounds is very high. However, the author is not limiting herself to simply those compounds. The paragraph discussed all the approaches which are under investigation at present which raises the number of possible combinations to a remarkable number. A reasonable expectation of success is required to reject claims as *prima facie* obvious. Buttle does not motivate one of ordinary skill in the art to make the claimed combination of sibutramine and orlistat, much less its use to treat co-morbid conditions.

Wilding discloses that sibutramine and orlistat respectively have similar efficacy to dexfenfluramine and result in a weight loss of up to 10%. It does not suggest the combination of sibutramine and orlistat to treat co-morbid conditions and it does not teach synergy between sibutramine and orlistat. Based upon the fact that each drug individually has the same effect on weight loss, one of ordinary skill would not be motivated to combine the two compounds to get synergistic effect. One would not expect to see an advantage in combining two drugs of equal effect. Further, the teaching that obesity can be treated by either sibutramine or orlistat alone does not suggest that co-morbid conditions can be treated by the combination of the two drugs.

MPEP 2145 states "A prior art reference that 'teaches away' from the claimed invention is a significant factor to be considered in determining obviousness...". Support for the position that Buttle and Wilding do not provide motivation to a person skilled in the art to try the particular combination of sibutramine and orlistat comes from the article in the New York Times, 15 May 1997, quoted in the instant specification on page 1, lines 31-32 stating that sibutramine and orlistat should not be combined.

The Examiner alleges that because the references teach the treatment of obesity in general and as such, it is believed that the skilled artisan would have readily recognized that pathophysiological sequela of obesity would also be effectively treated. Applicants list several examples of "co-morbid conditions", including non-insulin dependent diabetes mellitus, impaired glucose tolerance, hypertension, stroke, cerebral ischaemia and panic attacks. Each of these is recognized as a distinct disease. For each of these conditions, therapies have been developed specifically for that particular condition. A medical professional would be inclined to utilize these first-line medications to treat the individual ailment. A practitioner would not be motivated by the art to use a weight loss drug for any of these conditions.

As further evidence that the combination of sibutramine and orlistat is not obvious, Applicants submit, as Exhibit 1, a copy of Rule 132 Declaration signed by David John Heal, inventor of the instant application. This Declaration was originally submitted in a related case, namely U.S. Serial Number 09/212,249, subsequently granted as U.S. Patent 6,403,641. In this Declaration, Dr. Heal reports the results of a study involving rats treated with orlistat alone, sibutramine alone or treated with orlistat and pair-fed with the sibutramine-treated group. The unexpected result of these studies is that the rats pair-fed with the sibutramine-treated group exhibited profound weight-loss significantly greater than that of either sibutramine or orlistat when given alone.

Applicants maintain that taking the prior art as a whole there was no motivation to combine sibutramine and orlistat and there is no motivation to use the combination for treating co-morbid conditions. Further, the results in the Declaration demonstrate the unexpected potential for synergy with the combination of the present invention, which is not disclosed or suggested by Buttle or Wilding.

Based upon the foregoing, Applicants submit that the rejection of claims 1-8 over Buttle and Wilding under 35 U.S.C. §103(a) is obviated and should be withdrawn.

No fees are due for the instant amendment since the total number of claims after entry of the amendments hereinabove is not more than the total number of claims that Applicants have paid for to date.

Based upon the foregoing, Applicants believe that claims 1-8 are in condition for allowance. Prompt and favorable action is earnestly solicited.

If the Examiner believes that a telephone conference would advance the condition of the instant application for allowance, Applicants invite the Examiner to call Applicants' agent at the number noted below.

Respectfully submitted,

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Gayle O'Brien

Gayle O'Brien
Agent for Applicants
Reg. No. 48,812

Abbott Bioresearch Center
100 Research Drive
Worcester, MA 01605
(508) 688-8053